REMARKS

This paper is responsive to the Office Action dated December 18, 2003, which is the fifth non-final action on the merits of the application. By way of this amendment, claim 16 is cancelled and claim 32 is added. Accordingly, claims 1-14, 18-20, and 22-32 are under examination in this application.

Applicant is grateful for withdrawal of rejections under 35 USC § 102(b) with respect to U.S. Patent 5,837,233 (Granger); under 35 USC § 102(a) and (f) with respect to International Patent Publication WO 98/16238; and under 35 USC § 103(a) with respect to a publication by Kruse et al. (J. Neuro-Oncology 19:161, 1994). The claims under examination now stand newly rejected as not patentable over the combination of the Granger patent and the WO 98/16238 application.

Reconsideration and allowance of the application in view of the amendments and remarks made in this paper is respectfully requested.

Claim Amendments

The amendments to the claims do not new matter to the disclosure. Examples 6 and 7 illustrate treatment of a tumor according to the invention, wherein the treatment is resectable (e.g., page 58, line 15 ff.), but is nonetheless left at the site at the time of the first injection of alloactivated lymphocytes (either in whole or in part), to enable the administration of the second injection of alloactivated lymphocytes. Other illustrations of the practice of the invention in this fashion are provided elsewhere in the disclosure.

Interview Summary

Applicant wishes to express gratitude to Dr. Shin-Lin Chen for the helpful and constructive interview with the undersigned conducted at the Patent Office in March.

This response incorporates the suggestions made by the Examiner at the interview. The application is believed to be in condition for allowance, which is respectfully requested.

Claim Objection

Claim 16 is provisionally objected to under 37 CFR § 1.75 as being a substantial duplicate of claim 10. By way of this amendment, claim 16 has been cancelled. Applicant thanks the Examiner for finding this unintended duplication.

Rejection under 35 USC § 112

Claims 10 and 16 stand rejected under § 112 ¶ 2 as being indefinite for reciting the phrase: "removing any residual tumor at or around the site of the second cell population at a time subsequent to when the second cell population was implanted".

Claim 16 has now been cancelled.

Applicant respectfully submits that claim 10 is clear and definite in their present form. Specifically, claim 1 requires that both the first and second population of alloactivated lymphocytes be administered in or around the site of a resectable tumor. The first cell population is administered in a manner that tumor is left at the site. Leaving tumor cells at the site of the first administration allows the practicing clinician to administer the second population of cells into the same place. However, following administration of the second cell population, it is not necessary for the clinician to leave tumor cells at the site any further, unless a third population of alloactivated cells is to be administered to the same site at a later time. Claim 10 allows for the possibility that the clinician may wish to resect the tumor as no longer needed, concurrently with administration of the second cell population. Without intending to be limited by theory, it is believed that there is enough tumor antigen shed or otherwise left at the site to act as bystander antigen in concert with the second cell population, as long as treatment is administered to the site without delay.

Rejections under 35 USC § 103

Claims 1-10, 12-14, 16, 19-20, and 22-31 stand newly rejected under § 103(a) as being obvious over U.S. Patent 5,837,233 (Granger) in combination with published PCT application WO 98/16238. Claims 11 and 18 stand rejected under § 103(a) as being unpatentable over the same two references, when further combined with references by Feldhaus et al., and Haugland.

Applicant respectfully disagrees. As indicated previously, the Granger application does not teach or fairly suggest the administration of multiple doses of alloactivated cells *to a single patient.* Reference to dose escalation in the Granger disclosure must be interpreted in the context of the rest of the disclosure. The patients receive only a single dose of alloactivated cells (Example 2). Ergo, determination of the optimal dose according to the Granger disclosure involves evaluating the effect of different dose levels *in different patients.*

The Office Action attempts to make up the features missing from the Granger patent by combining it with the WO 98/16238 application. However, there is no motivation for the skilled reader to combine the two references, because they refer to different inventions that are administered to cancer patients in a different way and are directed towards a different object.

Accompanying the response filed in this application on October 2, 2002 was a Declaration under 37 CFR § 1.132 by John Hiserodt, M.D. Dr. Hiserodt explains that the present application is an improvement of the Granger method, and which is *different in nature and practice* from what is described in WO 98/16238. Specifically, the WO 98/162388 application describes a vaccine containing both alloactivated lymphocytes *and tumor antigen,* designed for administration at a site *away from the primary tumor.* Like other vaccines, it may be administered in multiple doses to boost or enhance the immunological response. The tumor antigen in the WO 98/162388 application is typically give in the form of tumor cells *which have been irradiated or otherwise inactivated to prevent proliferation.*

In contrast, the system described in the Granger patent involves administering alloactivated cells *directly into the tumor bed,* without any added tumor antigen. Instead, the tumor itself provides a source of bystander antigen, in the form of live tumor cells or their products. The Granger patent shows that a *single administration* of the implant is *fully effective* in eliciting an immune response and providing the patients with a therapeutic effect against their cancer. If the tumor is resectable, then the implant is administered *at about the time the tumor is removed* (Col. 10 line 66 ff).

Dr. Hiserodt further explains that the present application teaches that administering a second alloactivated cell population into the tumor site at a subsequent time has a surprising additional benefit. It can augment regression of the tumor and substantially prevent occurrence of metastases.

Contrary to standard clinical practice, this new invention teaches the clinician that it is actually beneficial to *leave tumor in the patient,* in order to provide bystander antigen for the second administration of alloactivated cells. For this reason, claim 1 and its dependents are patentable over the Granger patent — which cannot be fairly combined with the vaccine technology of the WO 98/16238 application.

To advance prosecution of this application, claim 1 has been amended to indicate that tumor is left behind at the site, *even though the tumor is resectable.* This is contrary to standard clinical practice, and goes beyond what is described in the Granger patent. Accordingly, claim 1 and its dependents are patentable over the prior art of record.

Claim 23 and its dependents are distinguished over the Granger patent because of the requirement that the second population of alloactivated cells is administered into a tumor site between 1 and 8 weeks after the implanting of the first cell population. As indicated previously, even if a clinician would be motivated to administer a second dose upon determination that a first dose had failed, the period of 1 to 8 weeks is inadequate to determine whether or not the first dose had failed.

The Office Action indicates that in Figure 2 of the Granger patent, tumor volume of 4 patients (Schmidt, Howland, Benge, and Reddy) remain the same after 3-4 weeks, and the tumor volume of Lavender starts to increase after about 3-4 weeks. This is in fact incorrect, *since there is only one volume measurement for any of the patients* between removal of the primary tumor, and the 8 week time point. At 10 weeks, Schmidt, Howland, Benge, and Reddy show no increase in image volume, *which can be interpreted as showing that the treatment is successful,* since the residual volume has been stabilized and there is no sign of tumor growth. The change in image volume for Lavender is less than 10%, which can hardly be viewed as a substantial increase. Patients Lundy and Jacobson show minimal change in volume in the first two measurements after resection, but continue to show volume reduction for several weeks further. The combined results show that determination of the effect of the administered cells is uncertain at best.

Most significantly, it appears that *none of the patients received a second dose of alloactivated cells,* regardless of whether the long-term trend in image volume was upwards or downwards sloping. If Granger as inventor of this technology did not himself believe that administration of a second alloactivated cell population was indicated at any time, then there is no suggestion to the reader that a second administration would have any benefit.

In contrast, the invention referred to in claim 23 of this application requires that every patient treated according to the invention receive a second administration of alloactivated cells between 1 and 8 weeks of the first, *even though the effect of the first dose will be uncertain, and regardless of the ultimate effect of the first dose.*

Withdrawal of this rejection is respectfully requested.

Applicant disagrees that there is motivation to combine the Granger Patent and the WO 98/16238 application with the references by Feldhaus et al. and Haugland, or that the combination affects the patentability of Claims 11 and 18. Removal of the Granger patent and WO 98/16238 as references for the reasons already explained is sufficient to overcome the rejection of these claims, and no further comments are needed.

For all of these reasons, applicant respectfully submits that the pending claims are patentable over the prior art of record.

Request for Examiner's Affidavit

The Office Action indicates that "it as common practice at the time of the invention to have multiple administrations to ensure better results of a treatment" (page 7). However, what constitutes "common practice" is not explained. Of course, the typical use of a particular treatment modality will depend on the nature of the treatment. The invention claimed in this application is not a standard cancer treatment method, such as irradiation or a small molecule drug, nor is it a vaccine. The Granger patent provides a new paradigm in cancer therapy, wherein alloactivated lymphocytes are implanted directly into a tumor bed, in order to elicit a response in the host against the tumor.

Since this therapy was not known before issuance of the Granger patent, "common practice" of this type of therapy is not a matter of standard knowledge in the art. Accordingly, applicant requests an Examiner's Affidavit, pursuant to 37 CFR § 1.104(d)(2) and MPEP § 2144.03.

In the alternative, applicant requests that rejection of claim 23 under 35 USC § 103 be withdrawn.

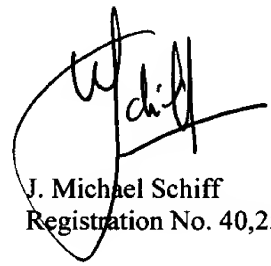
Request for a further Interview

Applicant requests that all outstanding rejections be reconsidered and withdrawn in light of this submission. The application is believed to be in condition for allowance, and prompt issuance of a Notice of Allowance is respectfully requested.

If upon consideration of this paper, the Examiner believes there are further matters to be addressed, applicant hereby requests an interview by telephone.

Should the Patent Office determine that a further extension of time or other relief is required for further consideration of this application, applicant hereby petitions for such relief and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of this document to the Credit Card indicated on accompanying PTO-2038.

Respectfully submitted,



J. Michael Schiff
Registration No. 40,253

808 Coleman Avenue, Suite 19
Menlo Park, CA 94025
Phone: 650-327-0960

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